JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Greater macrovascular and microvascular morbidity from type 2 diabetes in northern compared with southern China: A cross-sectional study

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Keywords
Macrovascular complication, Microvascular complication, Type 2 diabetes

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J Diabetes Investig 2020; 11: 1285–1294

doi: 10.1111/jdi.13262

Clinical Trial Registry
ClinicalTrials.gov
NCT01128205

ABSTRACT

Aims/Introduction: There are substantial differences in genes, diet, culture and environment between the northern and southern Chinese populations, which might influence treatment strategy and screening policy. We studied the differences in type 2 diabetes and diabetic complications between northern and southern China.

Materials and Methods: We carried out a cross-sectional survey using data from the China Cardiometabolic Registries on blood pressure, blood lipids and blood glucose in 25,398 Chinese type 2 diabetes patients. Macrovascular, microvascular and other complications were collected by self-report or medical records, and then divided into the northern and southern groups by the boundary of the Yangtze River.

Results: Northern patients were younger, and had heavier weight, greater body mass index and waist circumference, higher blood pressure, higher total cholesterol, higher low-density lipoprotein cholesterol, and higher hemoglobin A1C. The prevalence of cardiovascular, cerebrovascular and macrovascular complications were 1.76-fold, 1.24-fold and 1.47-fold more in northern than that in southern Chinese patients. In addition, the prevalence of diabetic nephropathy, retinopathy, neuropathy and microvascular complications in northern Chinese patients also increased. When stratified by age, the difference in both cardiovascular disease and ischemic stroke morbidity became significant, even in the 35–44 years age group.

Conclusions: More macrovascular and microvascular complications were found in northern compared with southern patients, and the largest difference also appeared in the younger age groups <55 years, which might be meaningful to a screening and treatment strategy according to geographic differences.

INTRODUCTION

The prevalence of type 2 diabetes varies widely in different regions and races. Many studies have suggested that genes and living environment play important roles in the pathogenesis of diabetes. Compared with the European population, the onset of diabetes is earlier and the body mass index (BMI) is lower in the Asian population[1-3]. The risk of diabetes varies by genes[4-6], geographical environment[7,8], diet[9,10] and living environment[11], as do its complications[12,13]. In China, the latest data on the epidemic of diabetes came from the national epidemiological survey in 2013. Because of the differences in statistical methods, the latest prevalence of diabetes was 10.9%[14], slightly lower than the 11.6% found by Ning *et al.*[15] However, these reports did not analyze the characteristics of diabetes in different regions of China. China has a large geographical area across a latitude of nearly 50° and latitude of 3°31′N to 53°33′N, which traditionally can be divided into northern and southern parts by the Yangtze River. Recently, several studies suggested that

Received 30 April 2019; revised 15 March 2020; accepted 23 March 2020

geography matters in the prevalence of diabetes and diabetic complications[16,17]. A meta-analysis also showed that the prevalence of diabetic retinopathy was higher in the northern compared with that in the southern Chinese population[18]. A cross-sectional survey of 634 patients with diabetic amputation procedures showed that the age of onset of diabetic foot ulcer was earlier in the northern than that in the southern Chinese population[19]. A recent study by Ji *et al.*[20] showed that there were geographical differences in cardiovascular disease and stroke among Chinese diabetes patients, with the highest prevalence in north and northeast China. However, that study did not analyze the effects of other characteristics of diabetes patients in different regions, such as microvascular disease, concomitant diseases or patient profiles, on clinical outcomes. A group from the Chinese Center for Disease Control and Prevention recently found that the geographical distribution of prediabetes in adults in China differed by geographic areas, and it significantly varied throughout the country[21].

The China Cardiometabolic Registries on Blood Pressure, Blood Lipid and Blood Glucose in Chinese Type 2 Diabetes Patients study was carried out to assess the level of control of blood glucose, blood pressure and blood lipids (3Bs) among patients with type 2 diabetes [22]. The patients were enrolled at hospitals representative of geographic regions, tiers and physician specialties in China. Using this database, we could observe the effects of the characteristics of type 2 diabetes in different areas, including concomitant diseases, macrovascular and microvascular complications, and patient profiles, on clinical outcomes.

The prevalence of diabetes has been increasing rapidly in China over the past 30 years. Because diabetes cannot be cured and because its complications are dangerous, the prevention of diabetes and related complications is a priority. Between northern and southern China, there are many differences in genes, diet, culture and living environment. These differences have a significant impact on the characteristics and complications of diabetes between the two regions. By using data from China Cardiometabolic Registries on Blood Pressure, Blood Lipid and Blood Glucose in Chinese Type 2 Diabetes Patients, we observed the characteristics of diabetes, and its macrovascular and microvascular complications between the northern and southern Chinese patients. We believe these findings will assist in the development of a more individualized prevention and treatment plan for northern and southern Chinese patients.

METHODS

Study design and participants

Data were obtained from the 3B study, an observational, cross-sectional, multicenter, multispecialty study of ambulatory patients with established type 2 diabetes carried out from August 2010 to March 2012. The patients aged ≥18 years had been diagnosed with type 2 diabetes for >6 months according to the World Health Organization criteria, as recommended by the Chinese diabetes guidelines, and were recruited at endocrinology, cardiology, nephrology and internal medicine clinics in 104 hospitals at different levels (i.e., tertiary hospitals, secondary hospitals and primary hospitals) across six major geographic regions of China, including northern China (Liaoning, Jilin, Shaanxi, Gansu Provinces and Beijing) and southern China (Sichuan, Guangzhou, Hunan, Jiangsu Provinces, Chongqing and Shanghai). Patients were excluded because of pregnancy, participation in any other clinical studies and unclear medical history reporting. The details of the study have been described elsewhere[22]. Written informed consent was obtained from each participant before data collection. This study was approved by the ethics committee of Peking University People's Hospital and by ethics committees at other hospitals where an individual committee review was required (registered at clinicaltrials.gov, No. NCT01128205).

Data collection

Self-reported information was collected from enrolled patients on demographic and socioeconomic characteristics, such as educational level, individual and family income, medical insurance, employment status, health behaviors (smoking, drinking and exercise), and whether they were diagnosed with any comorbidities or diabetic macrovascular complications (including cardiovascular, cerebrovascular or peripheral vascular disease), microvascular complications (including nephropathy, retinopathy or neuropathy), or other complications. Most patients had more than one diabetic complication, which were calculated into the complication. Furthermore, patients also reported individual and family medical history, previous diagnosis of hypertension or dyslipidemia, previous use of medication for hypertension or dyslipidemia, symptoms of hypoglycemia and current medications. "Smoking" was defined as smoking on average one or more cigarette daily for ≥1 year. "Drinking" was defined as consuming on average at least 50 g of alcohol daily for ≥1 year. A sedentary lifestyle was defined as not participating in regular physical activities. Income was classified into tertiles: high (≥CNY5,000/person/family/month), middle (CNY2,000–5,000/person/family/month), and lower middle (≤CNY2,000/person/family/month). Fasting serum glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C) and hemoglobin A1C (HbA1c) were measured. The target goals of HbA1c <7%, blood pressure (BP) <130/80 mm Hg, total cholesterol <4.5 mmol/L and LDL-C <2.6 mmol/L are consistent with the Chinese guidelines for diabetes prevention and treatment[23].

Statistical analysis

The statistical analysis was carried out using SPSS version 23 (IBM Corporation, Armonk, NY, USA). Descriptive statistics are presented for the normal variables as the mean ± standard deviation, and non-normal variables as medians and percentiles (25th percentile, 75th percentile). The numbers and variables were tested for significance using one-way analysis of percentages, and were reported for the categorical variables. Between-group disparities of continuous variance (ANOVA) or the Mann–Whitney *U*-test and the Pearson's ^{2}-test or Fisher's exact test were used for categorical data. The differences (%) in major cardiovascular events between the north and south were calculated as (prevalence in the north – prevalence in the south) / prevalence in the north × 100%. The Cochran–Mantel–Haenszel test was used to calculate the disparities (%) in major cardiovascular events between north and south China according to the age groups. The results are expressed as odds ratios with 95% confidence intervals. A statistically significant difference was considered at the two-tailed level of $P < 0.05$.

RESULTS

Patients' demographic and clinical characteristics between northern and southern China

A total of 26,493 patients with type 2 diabetes were enrolled. According to the exclusion criteria, 1,095 patients were excluded, and a final 25,398 patients were included in the analysis dataset, with an enrollment ratio of 95.9%.

Patients (25,398) were divided into northern and southern Chinese groups based on the Yangtze River (Table 1): with 11,932 patients in northern China (of whom 3061, 4377 and 4494 were from primary, secondary and tertiary care hospitals, respectively), and 13,466 patients in southern China (of whom 3452, 5067 and 4947 were from primary, secondary and tertiary care hospitals, respectively). There was no hospital-level difference in numbers of patients enrolled between northern and southern China.

The duration of diabetes was similar, and the median disease course was 6 years (2–11 years) from both regions. Compared with enrolled southern Chinese patients, northern Chinese patients were younger, and had an earlier age at diagnosis, heavier weight, greater BMI and larger waist circumference. Furthermore, compared with enrolled southern Chinese patients, northern Chinese patients had higher systolic BP, diastolic BP, total cholesterol, LDL-C and HbA1c. As for habits and culture, northern Chinese patients had a higher proportion of smoking and drinking habits, lower proportion of exercise, and higher educational level. In terms of income, northern Chinese patients had a higher proportion of middle-class incomes and a lower proportion of high/low-class incomes.

Among northern Chinese patients, a total of 72.3% achieved BP control, 41.4% achieved LDL-C control, 40.9% achieved HbA1c control and 14.0% achieved all the 3B target goals compared with 75.5%, 44.6%, 47.9% and 17.7% among southern Chinese patients, respectively ($P < 0.001$). As compared with southern patients, northern patients were 95.8%, 92.8%, 85.4% and 79.1% as likely to achieve BP control, LDL-C control, HbA1c control and all of the 3B targets goals, respectively.

Combined control of risk factors between northern and southern Chinese patients stratified by age

The proportion who achieved BP control decreased gradually with increasing age both in northern and southern patients. There was no difference in the proportion who achieved BP control between the two regions in patients aged <35 years. Furthermore, the proportion who achieved BP control was lower in northern than that in southern patients aged >35 years (Figure 1a).

The proportion who achieved LDL-C control from both regions showed an approximate U-shaped curve, with the highest proportion aged >75 years. The proportion who achieved LDL-C control was significantly lower in northern than that in southern patients in the 45–54 years and 65–74 years age groups (Figure 1b).

In both northern and southern patients, the proportion who achieved HbA1c control increased gradually with increasing age, and the peak in the 65–74 years age group was followed by a slight decrease in the group aged >75 years. Similar to the LDL-C results, the proportion who achieved HbA1c control was significantly lower in northern than that in southern patients in every age group (Figure 1c).

As for the 3B target goals, there was no difference between the two regions in the group aged <35 years. However, the proportion who achieved 3B target goal control was lower in northern than that in southern patients who were aged >35 years (Figure 1d).

Comorbidities and diabetic complication rates between northern and southern Chinese patients

There were also differences between northern and southern Chinese patients for comorbidities (Table 2). The prevalence of hypertension in northern Chinese patients was lower than that in southern Chinese patients ($P < 0.001$). In addition, the prevalence of dyslipidemia in northern Chinese patients was 1.34-fold more ($P < 0.001$) than that in southern Chinese patients. Furthermore, the prevalence of concomitant hypertension and dyslipidemia in northern Chinese patients was 1.51-fold more ($P < 0.001$) compared with that in southern Chinese patients.

Surprisingly, the prevalence of cardiovascular, cerebrovascular and all macrovascular complications in northern Chinese patients was 1.76-fold ($P < 0.001$), 1.24-fold ($P < 0.001$) and 1.47-fold ($P < 0.001$) more than that in southern Chinese patients, respectively. However, the prevalence of peripheral vascular disease in northern Chinese patients was lower than that in southern Chinese patients ($P = 0.027$). Also, the prevalence of diabetic nephropathy, retinopathy, neuropathy and all microvascular complications in northern Chinese patients was 1.12-fold ($P < 0.001$), 1.04-fold ($P = 0.176$), 1.30-fold ($P < 0.001$) and 1.13-fold ($P < 0.001$) more than that in the southern Chinese patients.

Prevalence of diabetic complications between northern and southern Chinese patients stratified by age

As shown in Figure 2, the prevalence of most diabetic macrovascular and microvascular complications was higher in northern than that in southern patients. Age stratification of

Table 1 | Comparison of diabetes patient characteristics between northern and southern China

	Total	Northern	Southern	χ^2/*t*/*Z*	*P*
n (%)	25,398	11,932 (47.0)	13,466 (53.0)		
Hospital level, *n* (%)					
Primary	6,513 (25.6)	3,061 (25.7)	3,452 (25.6)	2.982	0.225
Secondary	9,444 (37.2)	4,377 (36.7)	5,067 (37.6)		
Tertiary	9,441 (37.2)	4,494 (37.7)	4,947 (36.7)		
Age (years)	62.6 ± 11.91	61.64 ± 11.88	63.45 ± 11.87	12.109	<0.001
Age group, *n* (%)					
≥65	11,565 (45.5)	5,056 (42.4)	6,509 (48.3)	90.706	<0.001
Sex, *n* (%)					
Male	11,944 (47.0)	5,807 (48.7)	6,137 (45.6)	24.301	<0.001
Ethnicity, *n* (%)					
Han	24,943 (98.2)	11,609 (97.3)	13,334 (99.0)	107.215	<0.001
Age at diabetes diagnosis (years)	54.55 ± 11.86	53.56 ± 11.86	55.43 ± 11.79	12.616	<0.001
Diabetes duration (years)	6 (2–11)	6 (2–11)	6 (2–11)	1.102	0.27
Weight (kg)	65 (59–74)	69 (60–76)	63 (55–70)	11.271	<0.001
BMI (kg/m^2)	24.61 (22.52–26.84)	25.08 (23.03–27.34)	24.17 (22.06–26.37)	6.432	<0.001
SBP (mmHg)	133 ± 16.34	133.58 ± 16.03	132.48 ± 16.59	5.347	<0.001
DBP (mmHg)	78.77 ± 10.08	79.97 ± 9.05	77.71 ± 10.8	18.017	<0.001
TC (mmol/L)	4.97 ± 1.45	4.99 ± 1.28	4.95 ± 1.59	2.093	0.036
LDL-C (mmol/L)	2.83 ± 1	2.86 ± 0.97	2.8 ± 1.03	4.807	<0.001
HDL-C (mmol/L)	1.3 ± 0.48	1.31 ± 0.52	1.3 ± 0.44	1.638	0.101
TG (mmol/L)	1.56 (1.1–2.27)	1.61 (1.13–2.33)	1.5 (1.06–2.22)	8.995	<0.001
HbA1c (%)	7.65 ± 2.05	7.8 ± 2.04	7.51 ± 2.06	11.307	<0.001
†Smoking, *n* (%)	4,168 (16.4)	2,183 (18.3)	1,985 (14.7)	58.268	<0.001
†Drinking, *n* (%)	2,019 (8.0)	1,147 (9.6)	872 (6.5)	85.091	<0.001
Exercise, *n* (%)					
No	11,069 (43.6)	4,865 (40.8)	6,204 (46.1)	72.243	<0.001
Frequent/PRN	14,329 (56.4)	7,067 (59.2)	7,262 (53.9)		
Education, *n* (%)					
Illiteracy	1,679 (6.6)	575 (4.8)	1,104 (8.2)	549.791	<0.001
Elementary school	5,649 (22.2)	2,071 (17.4)	3,578 (26.6)		
Middle school	11,907 (46.9)	5,918 (49.6)	5,989 (44.5)		
High school	3,929 (15.5)	2,067 (17.3)	1,862 (13.8)		
College level	2,234 (8.8)	1,301 (10.9)	933 (6.9)		
Income, *n* (%)					
Low	14,811 (58.3)	6,555 (54.9)	8,256 (61.3)	344.011	<0.001
Medium	8,775 (34.6)	4,726 (39.6)	4,049 (30.1)		
High	1,096 (4.3)	463 (3.9)	633 (4.7)		
Blood pressure control achieved, *n* (%)	18,801 (74.0)	8,630 (72.3)	10,171 (75.5)	33.786	<0.001
Lipid control achieved, *n* (%)	10,938 (43.1)	4,937 (41.4)	6,001 (44.6)	26.222	<0.001
Glucose level control achieved, *n* (%)	11,322 (44.6)	4,877 (40.9)	6,445 (47.9)	125.042	<0.001
Glucose level/lipid/blood pressure control achieved, *n* (%)	4,051 (16.0)	1,664 (14.0)	2,387 (17.7)	67.443	<0.001

Data are the mean (standard deviation), median (interquartile range) or *n* (%); *t* is the *t*-value of two independent sample *t*-tests, χ^2 is the χ^2 value of Pearson's χ^2-test, *Z* is the *Z*-value of the Mann–Whitney *U*-test. †Includes previous smoking or drinking history (non-smoker, ex-smoker, 1–5 cigarettes per day or ≥6 cigarettes per day; and non-drinker, ex-drinker, 1–10 g alcohol per day or ≥11 g alcohol per day). Targets of glycemic control were defined as glycated hemoglobin (HbA1c) of <7% whether patients were taking oral antidiabetic drugs or insulin or not. Targets of blood pressure control were defined as systolic blood pressure (SBP)/diastolic blood pressure (DBP) <140/90 mmHg whether patients were taking antihypertensive drugs or not. Targets of lipid control were defined as total cholesterol (TC) <4.5 mmol/L and low-density lipoprotein cholesterol (LDL-C) <2.6 mmol/L whether patients were taking lipid-lowering drugs or not. BMI, body mass index; PRN, three times/week; TG, triglycerides.

these complications showed that the prevalence of macrovascular complications increased with increasing age from both territories. The prevalence in the north was 2.03-fold more ($P = 0.008$) in the 35–44 years age group, 2.28-fold more ($P < 0.001$) in the 45–54 years age group, 2.14-fold more in the 55–64 years age group ($P < 0.001$), 1.96-fold more in the 65–74 years age group ($P < 0.001$) and 1.53-fold more in the >75 years age group ($P < 0.001$) compared with the prevalence

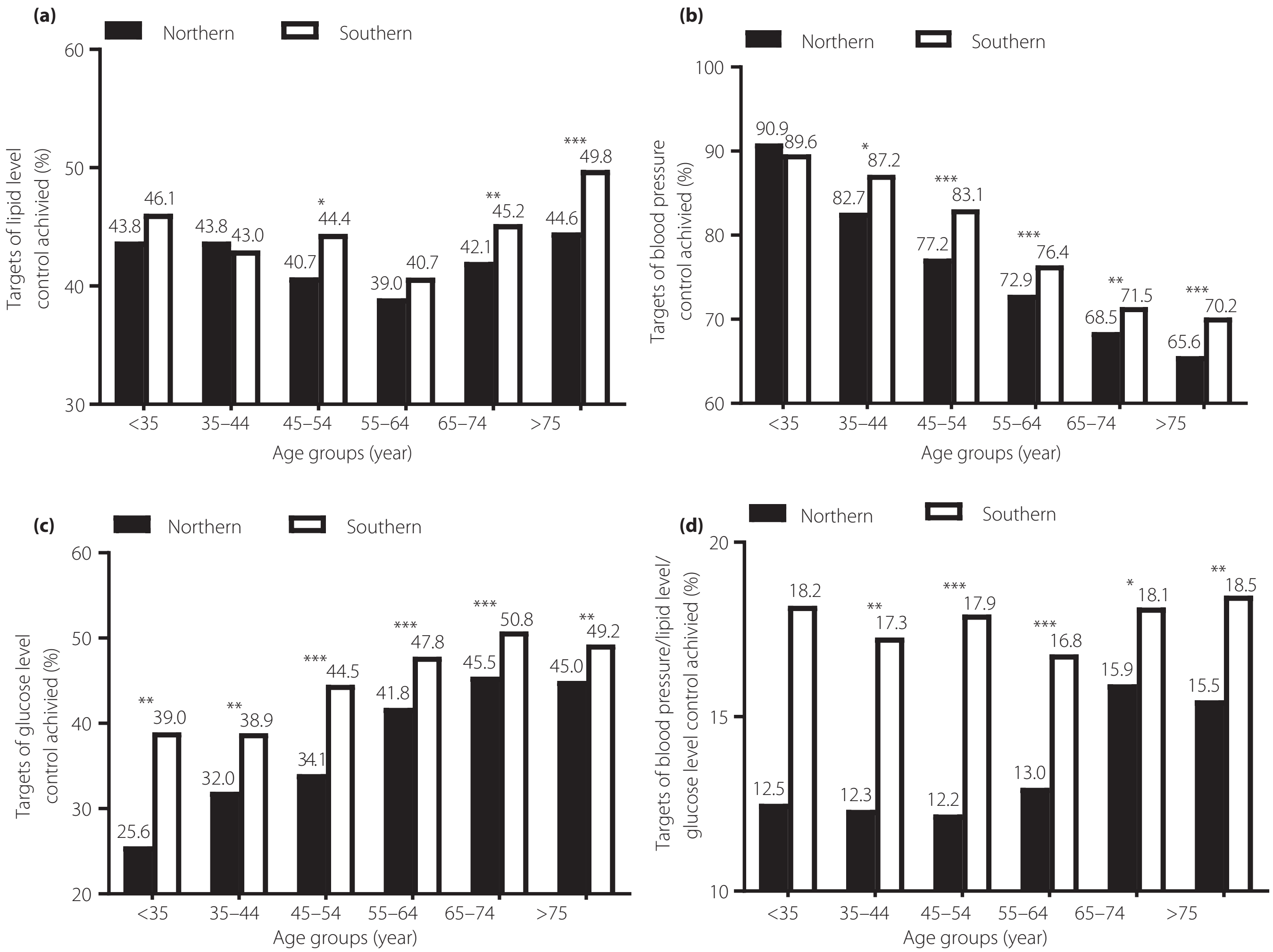

Figure 1 | Combined control of risk factors between northern and southern China stratified by age. (a) For achieved low-density lipoprotein cholesterol control: $P = 0.668$ for the group aged <35 years, $P = 0.777$ for the group aged 35–44 years, $P = 0.012$ for the group aged 45–54 years, $P = 0.117$ for the group aged 55–64 years, $P = 0.007$ for the group aged 65–74 years and $P < 0.001$ for the group aged >75 years. (b) For achieved blood pressure control: $P = 0.691$ for the group aged <35 years, $P = 0.018$ for the group aged 35–44 years, $P < 0.001$ for the group aged 45–54 years, $P < 0.001$ for the group aged 55–64 years, $P = 0.007$ for the group aged 65–74 years and $P = 0.001$ for the group aged >75 years. (c) For achieved glycated hemoglobin control: $P = 0.009$ for the group aged <35, $P = 0.007$ for the group aged 35–44 years, $P < 0.001$ for the group aged 45–54 years, $P < 0.001$ for the group aged 55–64 years, $P < 0.001$ for the group aged 65–74 years and $P = 0.005$ for the group aged >75 years. (d) For achieving all of the 3B target goals: $P = 0.151$ for the group aged <35 years, $P = 0.009$ for the group aged 35–44 years, $P < 0.001$ for the group aged 45–54 years, $P < 0.001$ for the group aged 55–64 years, $P = 0.014$ for the group aged 65–74 years and $P = 0.009$ for the group aged >75 years.

in the corresponding age groups in southern patients (Figure 2a).

As for ischemic stroke, compared with the south, the prevalence in northern Chinese patients was 2.33-fold ($P < 0.001$) among patients aged 45–54 years, 1.83-fold ($P < 0.001$) among patients aged 55–64 years and 1.40-fold ($P < 0.001$) among patients aged 65–74 years (Figure 2b).

The prevalence of macrovascular diseases in northern Chinese patients was 1.69-fold ($P = 0.018$) in the 35–44 years age group, 1.99-fold ($P < 0.001$) in the 45–54 years age group, 1.89-fold ($P < 0.001$) in the 55–64 years age group, 1.63-fold ($P < 0.001$) in the 65–74 years age group and 1.22-fold ($P < 0.001$) among patients aged >75 years, as compared with that in southern patients (Figure 2c).

The prevalence of diabetic nephropathy in northern Chinese patients was 1.54-fold more ($P = 0.002$) in the 35–44 years age group, 1.36-fold more ($P < 0.001$) in the 45–54 years age group and 1.15-fold more ($P = 0.022$) in the 55–64 years age group, as compared with that in southern patients (Figure 2d). Compared with the south, the prevalence of diabetic retinopathy in northern China was 1.12-fold ($P = 0.006$) in the 65–74 years age group and 1.21-fold ($P < 0.001$) in patients aged >75 years

Table 2 | Comorbidities and complications of diabetes patients between northern and southern China

	Total	Northern	Southern	χ^2	*P*
n	25,398	11,932	13,466		
Comorbidities				445.545	<0.001
Hypertension only	8,732 (34.4)	3,676 (30.8)	5,056 (37.6)		
Dyslipidemia only	2,790 (11.0)	1,514 (12.7)	1,276 (9.5)		
Hypertension and dyslipidemia complication	5,659 (22.3)	3,240 (27.2)	2,419 (18.0)		
CVD	4,111 (16.2)	2,504 (21.0)	1,607 (11.9)	382.087	<0.001
CBD	2,202 (8.7)	1,157 (9.7)	1,045 (7.8)	29.956	<0.001
PVD	391 (1.5)	162 (1.4)	229 (1.7)	4.907	0.027
Macrovascular complications	6,040 (23.8)	3,419 (28.7)	2,621 (19.5)	294.784	<0.001
Nephropathy	3,680 (14.5)	1,839 (15.4)	1,841 (13.7)	15.474	<0.001
Retinopathy	4,527 (17.8)	2,168 (18.2)	2,359 (17.5)	1.833	0.176
Neuropathy	3,394 (13.4)	1,815 (15.2)	1,579 (11.7)	66.380	<0.001
Microvascular complications	9,364 (36.9)	4,674 (39.2)	4,690 (34.8)	51.278	<0.001

Comorbidities included hypertension only, dyslipidemia only and both conditions. Macrovascular complications included cardiovascular disease (CVD; including stable angina, unstable angina, myocardial infarction, percutaneous coronary intervention or underwent coronary bypass) cerebrovascular disease (CBD; including ischemic stroke, hemorrhagic stroke or transient ischemic attack) and peripheral vascular disease (PVD). Microvascular complications included nephropathy, retinopathy and neuropathy.

(Figure 2e).The prevalence of diabetic neuropathy diseases in northern Chinese patients increased 1.69-fold ($P < 0.001$) in the 45–54 years age groups, 1.45-fold ($P < 0.001$) in the 55–64 years age groups and 1.19-fold ($P = 0.003$) in the 65–74 years age groups, as compared with southern Chinese patients (Figure 2f).

Multifactor analysis of diabetic complications between northern and southern China

A six-variable model was adjusted by the different factors in Table 3. After adjusting by age, sex, ethnic origin, weight, BP, LDL-C, HbA1c, smoking, drinking, exercise, education, income and hospital level, the models still showed significant differences in diabetic macrovascular and microvascular complications between northern and southern Chinese patients.

DISCUSSION

We analyzed northern and southern Chinese type 2 diabetes patients' characteristics from the 3B database. Herein, we report that type 2 diabetes patients have differences in complications and other factors between the two regions. Patients from northern China on average have lower control rates of blood glucose, BP, blood lipids and overall 3B target goals versus patients from southern China. Meanwhile, patients from northern China have more microvascular and macrovascular event reports. Lower 3B control rates for patients from northern China in the present study might account for the observed increase in vascular complications. Among patients from northern China, neuropathy, nephropathy and retinopathy morbidity were 130% higher than that among patients in southern China. However, the increase of microvascular complications were more pronounced in some age groups only. Interestingly, compared with the increase of microvascular disease, the macrovascular morbidity in northern China increased even more in people aged >35 years. Furthermore, cardiovascular morbidity of patients from northern China was 2.27-fold of that in southern China in patients aged 45–54 years. The United Kingdom Prospective Diabetes Study showed that a 1% reduction in glycated hemoglobin reduces the risk of myocardial infarction, stroke and microvascular complications by 14%, 12% and 37%, respectively, in diabetes patients[24].

Lower BP also reduced the risk of diabetes complications. In type 2 diabetes patients, an average systolic BP decrease of 6 mmHg results in a decrease in the risk of coronary heart disease, cerebrovascular disease and kidney disease of 18%, 6% and 21%, respectively[25,26]. A meta-analysis showed that a 1-mmol/L reduction in LDL-C correlates with a 21% reduction in major adverse cardiovascular events[27]. After we took the results of other studies into account, the difference in 3B control rates alone could not account for the observed magnitude of difference in macrovascular morbidity between patients from northern China and those from southern China.

Several studies have implied that besides the 3B control rate, many other factors also contribute to microvascular and macrovascular morbidity, including age, duration of diabetes and weight[28-30]. Earlier exposure to hyperglycemia could lead to higher microvascular and macrovascular morbidity[31-33]. Studies also showed that age of onset is one of the key factors that predict diabetic microvascular diseases. A study implied that a diabetes history of 10 years is significantly related to diabetic retinopathy morbidity. According to Song *et al.*[34], having diabetes for at least 10 years correlates with a significantly increased risk of diabetic retinopathy. In addition, a meta-analysis showed that northern patients have more diabetic retinopathy morbidity than southern patients in China[18]. Consistent with this result, the present study showed that northern

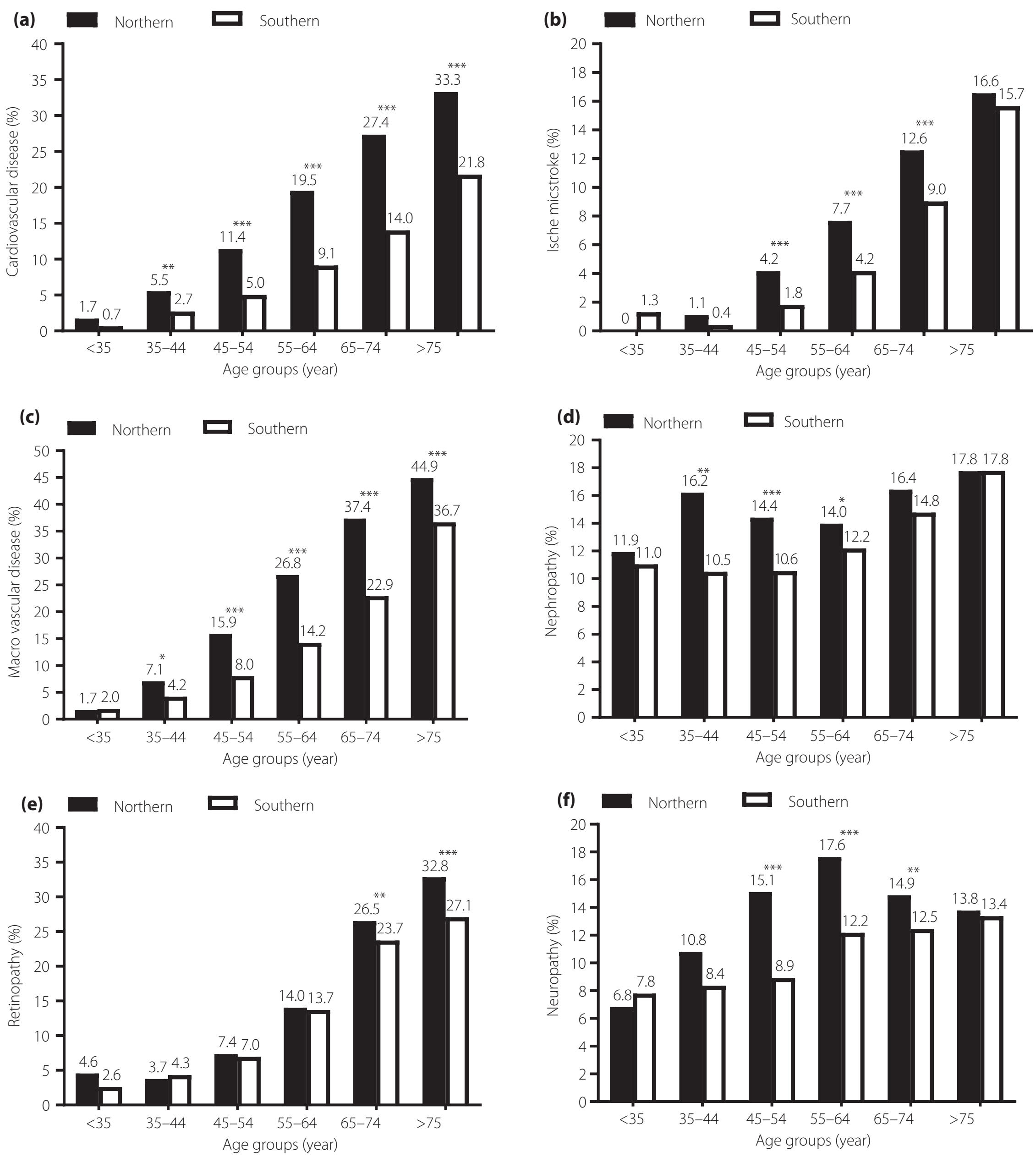

Figure 2 | Prevalence of diabetic complications between northern and southern China stratified by age. (a) For the prevalence of cardiovascular diseases: $P = 0.382$ for the group aged <35, $P = 0.008$ for the group aged 35–44 years and $P < 0.001$ for groups aged >45 years. (b) For the prevalence of ischemic stroke: $P = 0.129$ for the group aged <35 years, $P = 0.147$ for the group aged 35–44 years, $P < 0.001$ for the group aged 45–74 years and $P = 0.418$ for the group aged >75 years. (c) For the prevalence of macrovascular diseases: $P = 0.869$ for the group aged <35 years, $P < 0.018$ for the group aged 35–44 years and $P < 0.001$ for the groups aged >45 years. (d) For the prevalence of diabetic nephropathy: $P = 0{\cdot}800$ for the group aged <35 years, $P = 0.002$ for the group aged 35–44 years, $P < 0.001$ for the group aged 45–54 years, $P = 0.022$ for the group aged 55–64 years, $P = 0.056$ for the group aged 65–74 years, and $P = 0.983$ for the group aged >75 years. (e) For the prevalence of diabetic retinopathy: $P = 0.346$ for the group aged <35 years, $P = 0.581$ for the group aged 35–44 years, $P = 0.599$ for the group aged 45–54 years, $P = 0.628$ for the group aged 55–64 years, $P = 0.006$ for the group aged 65–74 years and $P < 0.001$ for groups aged >75 years. (f) For the prevalence of diabetic neuropathy: $P = 0.734$ for the group aged <35 years, $P = 0.116$ for the group aged 35–44 years, $P < 0.001$ for the group aged 45–54 years, $P < 0.001$ for the group aged 55–64 years, $P = 0.003$ for the group aged 65–74 years and $P = 0.696$ for the group aged >75 years. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Table 3 | Multifactor analysis of diabetic complications between northern and southern China

	Cardiovascular		Ischemic stroke		Nephropathy		Retinopathy	
	95% CI	*P*-value	95% CI	*P*-value	95% CI	*P*-value	95% CI	*P*-value
Model 1	2.188 (2.040–2.347)	<0.001	1.439 (1.312–1.578)	<0.001	1.177 (1.097–1.263)	<0.001	1.150 (1.076–1.229)	<0.001
Model 2	2.173 (2.026–2.331)	<0.001	1.430 (1.304–1.569)	<0.001	1.168 (1.088–1.253)	<0.001	1.154 (1.079–1.233)	<0.001
Model 3	2.166 (2.019–2.324)	<0.001	1.429 (1.302–1.567)	<0.001	1.165 (1.086–1.250)	<0.001	1.192 (1.114–1.277)	<0.001
Model 4	2.174 (2.026–2.333)	<0.001	1.409 (1.283–1.547)	<0.001	1.129 (1.051–1.212)	<0.001	1.179 (1.101–1.263)	<0.001
Model 5	2.171 (2.020–2.333)	<0.001	1.467 (1.332–1.616)	<0.001	1.133 (1.054–1.218)	<0.001	1.149 (1.072–1.232)	<0.001
Model 6	2.211 (2.057–2.377)	<0.001	1.491 (1.353–1.644)	<0.001	1.149 (1.068–1.236)	<0.001	1.154 (1.076–1.237)	<0.001

Data are odds ratio (95% confidence interval [CI]). *P*-value, northern compared with southern. The multivariable model was adjusted by different factors in the table. Multivariable model 1 was adjusted for age. Multivariable model 2 was adjusted for age, sex and ethnicity. Multivariable model 3 was adjusted for age, sex, ethnicity and weight. Multivariable model 4 was adjusted for age, sex, ethnicity, weight, blood pressure, low-density lipoprotein cholesterol and glycated hemoglobin. Multivariable model 5 was adjusted for age, sex, ethnicity, weight, blood pressure, low-density lipoprotein cholesterol, glycated hemoglobin, smoking, drinking, exercise education and income. Multivariable model 6 was adjusted for age, sex, ethnicity, weight, blood pressure, low-density lipoprotein cholesterol, glycated hemoglobin, smoking, drinking, exercise, education, income and hospital.

patients have more diabetic retinopathy morbidity than southern patients among those aged >65 years. For diabetic neuropathy, several factors, including duration of diabetes, waist circumference, systolic BP, LDL-C level and hypoglycemic therapies, are closely correlated[35,36].

Additionally, the bodyweight and BMI of northern Chinese patients are on average higher than those of southern Chinese patients. Several studies showed that bodyweight is correlated with macrovascular events. Obese people have shortened lifespans, and more macrovascular morbidity and mortality[37-40]. BMI has a close relationship with coronary heart disease death. Every 5-kg/m^2 increase of BMI leads to a 29% increase in coronary heart disease death[41]. BMI increase also leads to lower rates of control of blood lipids and BP[42]. In the present study, lower 3B control rates were found in northern than in southern Chinese patients.

After adjustment by age, sex, ethnic origin, weight, BP, LDL-C, HbA1c, smoking, drinking, exercise, education, income and hospital level, our multifactor analysis of diabetic complications between patients from northern and southern China did not find the key factors contributing to the difference in microvascular and macrovascular events.

Nevertheless, some limitations of the present study should be acknowledged. The possible explanatory factors not measured in this study include genome variation, diet, self-efficacy, self-care activities, effective screening process and efficacious antidiabetic therapy available. Some studies analyzed human genes in different regions of China and found a regional specificity in genome-wide copy number variation, which has been associated with an increased risk for some diseases[43]. However, the northern Chinese Han population primarily descends from the northern Mongolian race, whereas the southern Chinese Han population mainly descends from the southern Mongolian race, south Asian race and Far East transition race[44-46]. Genetic differences might affect the characteristics of diabetes. It is reported that the prevalence of hypertension is higher in northern than in southern China[47]. "The Educational Guide for Chinese Hypertension" describes the effects of sodium intake on BP between the northern and southern Chinese populations[48]. The staple foods of the northern population are cooked with wheat, beef and mutton. This diet leads to a higher sodium intake. By contrast, the southern population prefers cooked rice in staple foods, with a higher proportion of meat coming from seafood. As a result, these people consume less sodium[49-51]. These differences in diet also contribute to differences in metabolic disease distribution between the northern and southern Chinese populations[52,53].

In conclusion, more comorbidities, more macrovascular and microvascular complications, and lower 3B control rates were found in the northern compared with the southern type 2 diabetes patients. Further studies are required to explore these differences in order to initiate effective prevention strategies.

ACKNOWLEDGMENTS

This study was supported by the National Key Research and Development Program of China (Grant No. 2017YFC1309803), the Key Research and Development Program of Shaanxi Province, China (Grant No. 2017ZDCXLSF0201), and the National Natural Science Foundation of China (Grant No. 31571415). We thank LetPub (www.letpub.com) for its linguistic assistance during the preparation of this manuscript.

DISCLOSURE

The authors declare no conflict of interest.

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